Discordance Rates Between AMH and FSH in Different Age Groups

Farklı Yaş Gruplarında AMH ve FSH Arasındaki Diskordans Oranları

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Özet

Amaç: Farklı yaş gruplarına göre anti-Müllerian hormon (AMH) ve folikül stimülan hormon (FSH) arasındaki diskordans oranının Türk kadın kohortunda araştırılması. Gereç ve Yöntem: Bu retrospektif çalışma, Zeynep Kamil Eğitim Araştırma Hastanesi infertilite kliniğinde gerçekleştirildi. Hastalar; yaş gruplarına göre AMH ve FSH arasındaki diskordansı değerlendirmek amacıyla ≤30 yaş, 31-35 yaş, 36-39 yaş ve ≥ 40 yaş olmak üzere dört gruba ayrıldı. Diskordans oranı, AMH ve FSH median değerleri yaş gruplarına göre incelendi. Bulgular: Çalışmaya dahil edilme kriterlerini sağlayan 467 hasta çalışmaya dahil edildi. Hastaların %35.1'i (n=164) ≤ 30 yaş, %28.3'ü (n=132) 31-35 yaş arası, %22.7'si (n=106) 36-39 yaş arası ve %13.9'u (n=65) ≥40 yaş idi. Diskordans oranı normal AMH-anormal FSH değeri olan hastalar için ≤30, 31-35, 36-39, ≥40 yaş hasta grupları için sırasıyla %4.2, %6.7, %11.0, %17.9 olarak saptandı. Normal FSH-anormal AMH değeri olan hastalarda diskordans oranı ≤30, 31-35, 36-39, ≥40 yaş hasta grupları için sırasıyla %6.2, %8.5, %16.7, %17.9 olarak tespit edildi. Tartışma: Diskordans oranının normal AMH-anormal FSH değeri olan ve anormal AMH-normal FSH değeri olan Çalışmamızın sonuçları ve literatürdeki sonuçlara göre farklı etnik gruplarda AMH ve FSH arasındaki diskordans oranlarının ve yaşa göre AMH ve FSH düzeylerinin farklılık gösterebileceği düşünülmektedir.

Anahtar Kelimeler

Anti-Müllerian Hormon; Folikül Stimülan Hormon; Diskordans; Yaş

Abstract

Aim: To evaluate the discordance rates between anti-Müllerian hormone (AMH) and follicle stimulating hormone (FSH) levels according to different age groups in a cohort of Turkish women. Material and Method: This retrospective study was conducted at infertility clinics of Zeynep Kamil Training and Research Hospital. Patients were divided into 4 groups as ≤ 30 years, 31-35 years, 36-39 years, and ≥ 40 years to evaluate the discordance between AMH and FSH in terms of age. Discordance rates, and median level of AMH and of FSH were determined for each age group. Results: 467 patients who met the inclusion criteria were enrolled in the study. 35.1% (n=164), 28.3% (n=132), 22.7%(n=106), and 13.9% (n=65) of patients were ≤ 30 years, 31-35 years, 36-39 years, and ≥ 40 years, respectively. The discordance rates in terms of normal AMH but abnormal FSH level were 4.2%, 6.7%, 11.0%, 17.9% in the ≤ 30, 31-35, 36-39, ≥40 years age groups, respectively, whereas the discordance rates in terms of normal FSH but abnormal AMH levels were 6.2%, 8.5%, 16.7%, 17.9% in the same age groups, respectively. Discussion: Discordance rates steadily increased with advancing age both for concerning AMH-reassuring FSH and concerning FSH-reassuring AMH. Data from our study and the literature lead us to conclude that age-based AMH and FSH levels and also that discordance between these parameters may vary among different ethnic groups.

Keywords

Anti-Müllerian Hormone; Follicle Stimulating Hormone; Discordance; Age

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Introduction

Ovarian reserve tests have a significant role in predicting ovarian response to gonadotropin stimulation and to the outcome of assisted reproduction treatment (ART). Follicle stimulating hormone (FSH) and anti-Müllerian hormone (AMH) are the most commonly used ovarian reserve tests [1-3].

Early antral follicles secrete inhibin B and estradiol by stimulation of FSH. Inhibin B and estradiol result in FSH suppression through the feedback mechanism of the pituitary-gonadal axis. Levels of inhibin B and estradiol decrease after diminishing the ovarian follicle reserve and these changes cause the FSH levels to increase [4]. AMH is a member of the transforming growth factor-b (TGF-b) superfamily of growth and differentiation factors. It is produced by granulosa cells of preantral and small antral follicles [5]. AMH and FSH levels reflect the ovarian reserve at different stages of the follicular process; the antral and postantral follicular developments are reflected by FSH whereas postprimordial preantral and early antral follicular developments are reflected by AMH [6,7].

Recently, conflicting results were reported in different studies evaluating the association between AMH and FSH. Some studies demonstrated consistency between AMH and FSH while others found significant discordance between these two ovarian reserve tests [6-10]. The discordance can complicate the prediction of ovarian response to gonadotropin stimulation and ART outcomes.

On the other hand, the different studies emphasize that the characteristics of the female reproductive system have significant variability depending on ethnicity. The variabilities of ovarian reserve tests (AMH, FSH) regarding ethnicity were demonstrated and the normograms of ovarian reserve tests were evaluated based on ethnicity [11,12]. Based on this evidence, we can conclude that the relationship between AMH and FSH might be affected by ethnicity.

Therefore, we aim to evaluate the relationship between AMH and FSH levels in a cohort of Turkish women.

Material and Method

This retrospective study was conducted at infertility clinics of our hospital. The study protocol was approved by the Local Research and Ethics Committee of our hospital. Data on patient age, basal serum estradiol, FSH, and AMH levels were collected from a hospital database. Patient diagnoses were obtained from their medical records according to International Classification of Disease (ICD) codes. Exclusion criteria were: > 45 and < 18 years of age, presence of endocrinologic abnormality, and menstrual irregularity. The cut-off value for estradiol level was accepted as 75 pg/ml to verify that the serum was taken in early follicular phase, thus decreasing the possibility of FSH suppression that could cause a mistake in the assessment of discordance rate. AMH level ≥ 0.8 ng/mL was accepted as normal according to the AMH assay manufacturer's instructions. The cut-off value for FSH level was accepted as 10 IU/L and basal FSH level > 10 IU/L was defined as abnormal.

The serum FSH was measured on the Architect 16000, with flexible assay protocol, competitive chemiluminescent immunometric enzyme immunoassay system. The FSH intra-assay coefficient of variation was approximately < 5%, and the inter-assay coefficient of variation was approximately 4%. AMH enzyme immunoassay (Beckman-Coulter) was used for the measurement of serum AMH levels (ng/mL). The intra-assay coefficient of variation was <10%.

Statistical analyses

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 11.5 software. Pearson's correlation analysis was used for the assessment of the correlation between parametric variables (age, AMH, FSH). Data were given as median (minimum-maximum) or percentage. A p-value ≤ 0.05 was considered statistically significant.

Result

In the present study, there were serum FSH and AMH results of 623 patients. The estradiol level of 123 patients was higher than 75 pg/ml and these patients were excluded because it was accepted that the serum was taken in the early follicular phase. 467 patients who met the inclusion criteria were enrolled in the study. Patients were divided into 4 groups as ≤ 30 years, 31-35 years, 36-39 years, and ≥ 40 years to evaluate the discordance between AMH and FSH in terms of age. 35.1% (n=164), 28.3% (n=132), 22.7%(n=106) and 13.9% (n=65) of patients were ≤ 30 years, 31-35 years, 36-39 years, and ≥ 40 years, respectively. The median values of the basal FSH and AMH levels of the age groups are given in Table 1.

Table 1. Clinical characteristics of patients

		Values (median, min-max)
Age (years)		34.0 (20.0-45.0)
FSH (mIU/ml)	≤30 years	5.56 (0.07 – 69.50)
	31-35 years	6.44 (0.09 – 66.75)
	36-39 years	7.16 (1.2 – 60.86)
	≥40 years	11.31 (0.45 – 85.68)
	All patients	6.47 (0.07- 85.68)
AMH (ng/ml)	≤30 years	2.75 (0.01 -18.89)
	31-35 years	1.39 (0.01 - 14.04)
	36-39 years	0.83 (0.01 - 13.05)
	≥40 years	0.18 (0.01 - 4.54)
	All patients	1.51 (0.01- 18.89)

The rate of abnormal FSH level among patients with normal AMH level was 7.5% while the rate of abnormal AMH level among patients with normal FSH level was 10.1%. There was a steady increase in discordance with advancing age both for concerning AMH-reassuring FSH and concerning FSH-reassuring AMH (Figs. 1 and 2). The discordance rates in terms of normal AMH but abnormal FSH level were 4.2 %, 6.7 %, 11.0 %, and 17.9 % in the ≤ 30, 31-35, 36-39, ≥40 years age groups, respectively, whereas the discordance rates in terms of normal FSH but abnormal AMH levels were 6.2%, 8.5%, 16.7%, and 17.9% in the same age groups, respectively.

The correlation between AMH, FSH levels and age was evaluated separately (Table 2). There was a significant correlation between AMH level and age (r= -0.359, p< 0.001); AMH level decreased with aging. There was a significant correlation (r= 0.195, p<0.001) between age and FSH level; FSH level increased with aging.

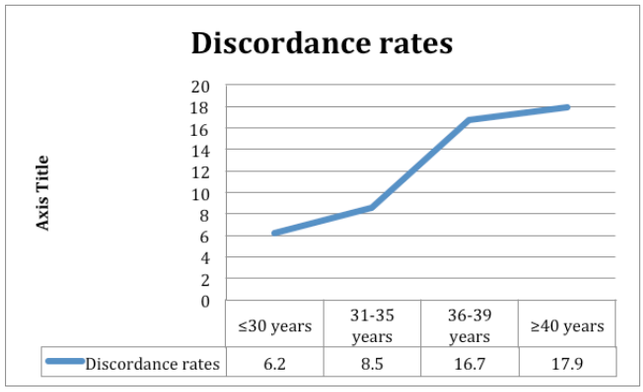

Fig 1. Discordance rates for concerning AMH-reassuring FSH in different age groups

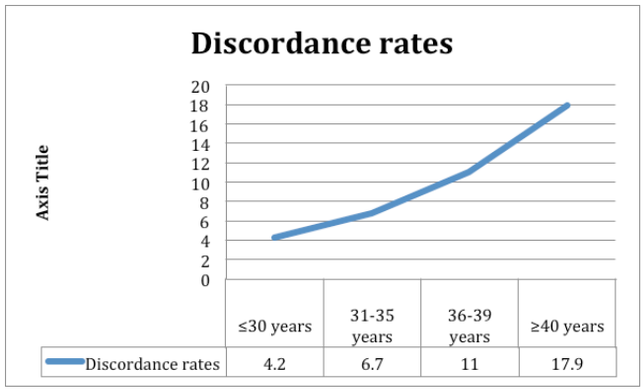

Fig 2. Discordance rates for concerning FSH-reassuring AMH in different age groups

Table 2. Correlations between serum AMH, FSH levels and the age

		Age	AMH	FSH
Age	r		-0,359	0,195
	p		<0.001	0.000
FSH	r	0.195	-0,315	
	p	0.000	<0.001	
AMH	r	-0,359		-0,315
	p	0.000		0.000

Pearson's correlation analysis was used
The level of significance was accepted at p = 0.05 level

Discussion

Our data showed that concordance and discordance between FSH and AMH varied between different age groups and that there was steady increase in discordance with advancing age both for concerning AMH-reassuring FSH and concerning FSH-reassuring AMH. Other studies have reported conflicting results about the consistency between AMH and FSH [6-10]. In addition, there is no adequate evidence in terms of discordance between these ovarian reserve tests and the implication of ethnicity on this discordance.

The relationship between AMH and FSH was assessed in a large study population by Leader et al. [9], where it was found that 6% of patients with reassuring AMH levels had abnormal FSH levels whereas 20% of patients with reassuring FSH levels had abnormal AMH levels. When analyzing discordance rate (FSH-reassuring but AMH concerning) according to age group, it was found to be 9.1% among patients < 35 years and 33.3% among patients aged ≥ 40 years. The discordance rates showed steady increase with aging. However, while the concerning FSH but reassuring AMH values were found to be consistent in approximately 5.6% of women, there was no statistically significant difference in rates of discordance among age groups. In conclusion, the authors stated that discordance between AMH and FSH levels was common and age dependent.

In the present study, it was found that 7.5% of patients with normal AMH levels had abnormal FSH levels while 10.1% of patients with normal FSH levels had abnormal AMH levels in whole study population. In addition, when analyzing based on age groups in our study population, discordance rates were 4.2%, 6.7%, 11.0%, and 17.9% in the ≤30, 31-35, 36-40, ≥40 years age groups, respectively, in terms of normal AMH but abnormal FSH level. In the same age groups, rates of normal FSH but abnormal AMH levels were 6.2%, 8.5%, 16.7%, and 17.9%, respectively.

The rate of discordance in patients with normal FSH but abnormal AMH levels was lower in our whole study population than in the outcomes of Leader et al. [9]. The discordance rate increased with aging in patients with reassuring AMH but concerning FSH level; this rate of increase was different than in the outcomes of Leader et al. This difference might be caused by several factors including different study populations with different genetic and environmental backgrounds, which could lead to a different ovarian biological age compared to chronological age [11,12]. That ethnicity could have a significant effect on ovarian reserve tests and ART outcomes is argued in the literature [11,13-17]. Basal FSH levels in African-American women were found to be higher than in age-matched white women [18-20]; moreover, AMH levels were found to be higher in white women compared to African-American and Hispanic women [21]. These studies support the independent effect of ethnicity on variation of basal hormone levels regarding ovarian reserve. These differences between discordance rates and their characteristics in our study population compared to those in other studies might be associated with the characteristics of the age-specific AMH normogram of the Turkish population. Age-related distribution of basal AMH level in the Turkish population was evaluated in a study by Ozcan et al [22], and the median AMH levels were 2.16 ng/ml, 2.15 ng/ml, 1.71 ng/ml, 0.8 ng/ml, and 0.47 ng/ml in the 20-24, 25-29, 30-34, 35-39, and ≥40 years age groups, respectively. In addition, the decline in AMH concentration started at the age of 30 and became more significant by age 35. An interesting finding of that study was that approximately 40% of women with AMH ≤1 ng/ml were ≤35 years in the Turkish population. In our study the median AMH levels were 2.75 ng/ml, 1.39 ng/ml, 0.83 ng/ml, and 0.18 ng/ml for the ≤ 30, 31-35, 36-39, and ≥ 40 years age groups, respectively. The median AMH levels of our study population according to age groups were similar to the results of the study by Ozcan et al [22].

Almog B et al.[23] evaluated age-related normograms of serum anti-Müllerian hormone levels in a population of infertile women from Europe and North America and the median AMH levels according to age groups. AMH levels were 2.1 ng/ml, 1.6 ng/ml, and 1.1 ng/ml in the 24-33, 34-38, and > 39 years age groups, respectively. The median AMH levels according to age groups

in European and North American populations are different from the median AMH levels of the Turkish population. Although the decrease of the AMH levels in European and North American populations seems to appear in a smoother pattern, in Turkish population this decrease occurs more rapidly with age.

One possible explanation of the frequent discordance between AMH and FSH might be related to the time difference between AMH decline and FSH increase; the AMH decline occurred at younger ages than the FSH increase [9]. In our study, we found that the AMH decline occurred earlier in a cohort of patients from the Turkish population when compared to characteristics of AMH decline in other populations. The differences in features of AMH decline among different populations may affect the discordance rates between AMH and FSH according to age groups.

Conclusion

Data from our study and the literature lead us to conclude that age-based AMH and FSH levels and also discordance between these parameters may vary among different ethnic groups. Due to these variations, in order to optimize the effectiveness of using discordance to predict ART outcome, population-specific cut-off values should be introduced and discordance should be evaluated according to the age group. A well-designed study is needed to reveal the clinical importance for ART outcomes of discordance between AMH and FSH levels.

Competing interests

The authors declare that they have no competing interests.

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